Objectives

- Describe the mechanism of action and pharmacology of chemotherapy agents and targeted therapies used for the treatment of hematologic and solid tumor malignancies

- Recognize common and unique adverse drug reactions of cancer therapies and associated prevention and management strategies

- Discuss additional information on administration, place in therapy, and/or unique drug properties
FDA approved 39 new drugs & biologics in 2012
- Most since 1996 (53)
- 2011 – 30
- 2010 – 21

Oncology drugs comprised of most approvals (11)

Five approvals so far in 2013

This presentation does not include information on new indications for existing agents
## Overview

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Company</th>
<th>Disease</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>Inlyta</td>
<td>Pfizer</td>
<td>RCC</td>
<td>1/27/12</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Erivedge</td>
<td>Genetech</td>
<td>Advanced Basal Cell Carcinoma</td>
<td>1/20/12</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Perjeta</td>
<td>Roche</td>
<td>HER2 Breast Cancer</td>
<td>6/8/12</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Kyprolis</td>
<td>Onyx Pharmaceuticals</td>
<td>MM</td>
<td>7/20/12</td>
</tr>
<tr>
<td>Ziv-aflibercept</td>
<td>Zaltrap</td>
<td>Sanofi</td>
<td>mCRC</td>
<td>8/3/12</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Xtandi</td>
<td>Astellas/Medivation</td>
<td>Castrate Resistant Prostate Cancer</td>
<td>8/31/12</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Bosulif</td>
<td>Pfizer</td>
<td>CML</td>
<td>9/4/12</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Stivarga</td>
<td>Bayer</td>
<td>mCRC</td>
<td>9/27/12</td>
</tr>
<tr>
<td>Omacetaxine mepesuccinate</td>
<td>Synribo</td>
<td>Teva Pharmaceuticals</td>
<td>CML</td>
<td>10/26/12</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Cometriq</td>
<td>Exelixis</td>
<td>Medullary Thyroid Cancer</td>
<td>11/29/12</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Iclusig</td>
<td>Ariad</td>
<td>CML/Ph+ALL</td>
<td>12/17/12</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Pomalyist</td>
<td>Celgene</td>
<td>MM</td>
<td>2/8/13</td>
</tr>
<tr>
<td>Ado-Trastuzumab Emtansine</td>
<td>Kadcyla</td>
<td>Genentech</td>
<td>HER2 mBreast Cancer</td>
<td>2/22/13</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Tafinlar</td>
<td>GSK</td>
<td>Melanoma</td>
<td>5/29/13</td>
</tr>
<tr>
<td>Trametinib</td>
<td>Mekinist</td>
<td>GSK</td>
<td>Melanoma</td>
<td>5/29/13</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Gilotrif</td>
<td>Boehringer Ingelheim</td>
<td>NSCLC</td>
<td>7/12/13</td>
</tr>
</tbody>
</table>
Other Notable Approvals

- Glucarpidase (Voraxaze) BTG International
  - Reduce toxic methotrexate levels
  - 1/17/12

- Vincristine Liposomal (Marqibo) Talon Therapeutics
  - Ph- ALL in 2\textsuperscript{nd} relapse
  - 8/9/12

- Radium (Ra) 223 dichloride (Xofigo) Bayer
  - Treatment of symptomatic bone mets in CRPC
  - 5/15/13
Vismodegib

- **Indication:** metastatic basal cell carcinoma or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation

- **Target:** Smoothened homologue (SMO; transmembrane protein in the Hedgehog signaling pathway)

- **MOA:** Hedgehog pathway regulates cell growth and differentiation in embryogenesis. Mutations in adults can lead to unrestricted proliferation in skin basal cells.

- **Dose:** 150 mg daily with or without food; do NOT make up a missed dose
Vismodegib

- Only available through specialty pharmacy
- Black box warning for birth defects, embryo-fetal death

Adverse effects
- Fatigue
- Alopecia
- Amenorrhea – reversibility unknown
- Abnormal taste, perception alterations; N/V/D/C
- Muscle spasm (72%), arthralgia

Drug Interactions: PPIs/Antacids; PgP Inducers/Inhibitors

Patients should not donate blood/products during and for 7 months after treatment
Pertuzumab

- Indication: for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

- Target
  - Extracellular dimerization domain of HER2

- Recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of HER2, and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4

- Mediates antibody-dependent cell-mediated cytotoxicity
Pertuzumab

- **Dosing**
  - 840mg IV over 60 minutes for loading dose followed by 420mg IV over 30-60 minutes every 21 days
  - Flat dose
  - Give loading dose again if > 6 weeks

- No dose adjustments, give or hold

- Give with trastuzumab

- **Adverse effects**
  - Cardiotoxicity
    - Hold if LVEF < 40% or if LVEF is 40-45% with a ≥ 10% drop from baseline
  - Hypersensitivity
  - Diarrhea
  - URI
  - Rash
  - Headache
  - Fatigue

- Black Box for embryo-fetal toxicity
Pertuzumab

- Order of administration
  - Pertuzumab and transtuzumab can be given in any order
  - Docetaxel is given AFTER trastuzumab and pertuzumab

- Loading dose of pertuzumab is given over 60 minutes and maintenance doses may be given over 30-60 minutes

- Patients should be observed 30-60 minutes after pertuzumab
Ado-Trastuzumab Emtansine

- **Target:** HER2

- **MOA**
  - HER2-antibody drug conjugate which incorporates the HER2 targeted actions of trastuzumab with the microtubule inhibitor DM1 (a maytansine derivative). The conjugate, which is linked via a stable thioether linker, allows for selective delivery into HER2 overexpressing cells, resulting in cell cycle arrest and apoptosis

- **Use**
  - In patients who previously received trastuzumab and a taxane, separately or in combination, and have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy

- **Dosing:** 3.6 mg/kg every 3 weeks
Ado- Trastuzumab Emtansine

- **Adverse Effects (>25%)**
  - Fatigue
  - Nausea
  - Musculoskeletal pain
  - Headache
  - Thrombocytopenia (Grade 3-4, 45% in Asians)
  - Constipation
  - Increased AST/ALT, Tbili

- **Black Box Warnings**
  - Hepatotoxicity
  - Cardiotoxicity
  - Embryo-fetal death
  - NOT interchangeable with conventional trastuzumab

- **CYP3A4 Substrate**

- **Other concerns**
  - ILD
  - Hypersensitivity
  - Extravasation
Ado-Trastuzumab Emtansine

- Ensure appropriate product is being administered

- Infuse over 90 minutes (first infusion) or over 30 minutes (subsequent infusions if prior infusions were well tolerated) through a 0.22 micron inline nonprotein adsorptive polyethersulfone filter

- Closely monitor infusion site during administration (extravasation has been reported; usually mild, within 24 hours of infusion)

- Monitor patient during infusion for signs of infusion-related reactions (eg, fever, chills); monitor for at least 90 minutes following initial infusion and (if tolerated) for at least 30 minutes following subsequent infusions
Place in Therapy

- HER2 Positive Disease; Metastatic Setting
- Pertuzumab: newly diagnosed patients with metastatic disease that have received no prior chemo; regimen is preferred by NCCN (category 1) for 1st line treatment
- Ado-Trastuzumab emtansine: Preferred agent (Category 1) for patients previously exposed to trastuzumab
Ziv-aflibercept

- Indication: for use in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) for the treatment of patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin containing regimen

- MOA: Acts as a soluble receptor (recombinant fusion protein) that binds to endogenous ligands VEGF-A, VEGF-B and PIGF inhibiting binding/activation of these receptors → decreased neovascularization and vascular permeability
Ziv-aflibercept

- Dose 4mg/kg IV Q 2 weeks
- Reduce dose for hypertension, proteinuria (2mg/kg)
- Black Box Warnings: hemorrhage, GI perforation, compromised wound healing
- Other ADEs: Fistula formation, arterial thromboembolic events, proteinuria, hypertension, RPLS (diarrhea, neutropenia), immunogencity
- Dehydration and diarrhea occur more in elderly patients
Ziv-aflibercept

- Infuse over 1 hour
- Administer prior to FOLFIRI
- Infuse via a 0.2 micron polyethersulfone filter; do not use filters made of polyvinylidene fluoride (PVDF) or nylon
- Administer with one of the following types of infusion sets: Polyvinyl chloride (PVC) containing DEHP, DEHP-free PVC containing trioctyl-trimellitate (TOTM), polypropylene, polyethylene lined PVC, or polyurethane
Regorafenib

- Indication: metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy; GIST patients previously treated with imatinib and sunitinib

- MOA/Targets
  - Inhibition of angiogenesis: VEGFR-1, -2, -3; TIE-2
  - Inhibition of tumor cell proliferation: PDGFR-alpha, -beta; FGFR-1,-2; p38 MAP kinase
  - Inhibition of oncogenesis: c-Kit; RAF-1
  - Other targets: BRAF, Ret, DDR2, Trk2A, Eph2A, SAPK2, PTK5

- 160 mg PO once daily with a low fat breakfast for the first 21 days of a 28-day cycle

- Available in 40 mg tablets
Regorafenib

- Take at the same time each day with a low fat breakfast that contains < 30% fat:
  - 2 slices of white toast with 1 tbsp of low-fat margarine and 1 tbsp jelly, 8 oz skim milk
    → 319 calories and 8.2 g fat
  - 1 cup cereal, 8 oz skim milk, 1 slice of toast with jam, apple juice, and 1 cup of coffee or tea
    → 520 calories and 2 g fat

- Store in the original bottle at room temperature (with desiccant)
  - Use within 28 days once bottle is opened

- Drug Interactions
  - CYP3A4 inducers and Inhibitors
  - UGT1A1 inhibition (Irinotecan)
  - Warfarin
Regorafenib

- Adverse Effects (>25%, CORRECT Trial)
  - Hand Foot Syndrome
  - Fatigue
  - Diarrhea
  - Anorexia
  - Voice changes
  - Hypertension
  - Mucositis
  - Rash

- Dose Adjustments for
  - Increased liver function tests
  - Hand Foot Syndrome
  - Hypertension

- Black Box Warning: Hepatotoxicity

- Other infrequent but serious AE:
  - Hemorrhage
  - Impaired wound healing
    - *Hold for 2 weeks prior to surgery*
  - GI perforation/fistula (0.8%)
  - Cardiac: MI, myocardial ischemia
  - Reversible posterior leukoencephalopathy syndrome (RPLS)
  - Secondary malignancies
    - keratoacanthoma/squamous cell carcinoma of the skin (0.09%)
Place in Therapy

- Metastatic colorectal cancer

- Ziv-aflibercept – must have progressed on an oxaliplatin based regimen (FOLFOX)

- Regorafenib – must have progressed on an fluoropyrimididine based, oxaliplatin based, irinotecan based, anti VEGF, and anti EGFR (if KRAS WT) therapy... think end of the line (3rd or later)
Enzalutamide

- Indication: metastatic castration-resistant prostate cancer who have previously received docetaxel

- MOA: Pure androgen receptor signaling inhibitor; unlike other antiandrogen therapies, it has no known agonist properties. It inhibits androgen receptor nuclear translocation, DNA binding, and coactivator mobilization, leading to cellular apoptosis and decreased prostate tumor volume.

- Dosing: 160 mg po daily with or without food

- Available as 40 mg capsules

- Not studied in severe renal/hepatic dysfunction
Enzalutamide

- Drug Interactions
  - Potential for severe interactions: Enzalutamide is a strong CYP3A4 and moderate CYP2C9 and CYP2C19 inducer
  - Major substrate of CYP2C8 and CYP3A4
  - **Dosage adjustment for concomitant strong CYP2C8 inhibitors:** Avoid concomitant use if possible. If coadministration is necessary, reduce enzalutamide dose to 80 mg once daily.

- Half Life – approximately 6 days
Enzalutamide

- Adverse Effects
  - Fatigue (51%)
  - Peripheral edema, Headache, Hot flashes (20%), Diarrhea (22%), Neutropenia (15%; grades 3/4: 1%), Back pain (26%), arthralgia (21%), musculoskeletal pain (15%), URI
  - Seizures observed in clinical trial – discontinue therapy

- Reproduction
  - Men using this medication should use a condom if having intercourse with a pregnant woman
  - A condom plus another effective method of birth control is recommended during therapy and for 3 months after treatment for men using this medication and who are having intercourse with a woman of reproductive potential
Cabozantinib

- Indication: progressive metastatic medullary thyroid cancer (MTC)
- MOA: Potent inhibitor of proinvasive receptor tyrosine kinases (RTKs), including AXL, FLT-3, KIT, **MET, RET, TIE-2, TRKB, and VEGFR-1, -2, and -3**; induces apoptosis of cancer cells and suppresses tumor growth, metastasis, and angiogenesis

- Absorption and Distribution: Tmax: 2-5hrs
  - Steady state achieved by Day 15 (for 140mg daily)
  - Highly protein bound in human plasma: >99.7%

- Metabolism and Elimination
  - Hepatic metabolism by CYP3A4 (80%) and CYP2C9 (~20%)
  - Half Life: 55 hours
Cabozantinib

- Recommended starting dosage: Cabozantinib 140mg on empty stomach
- Available strengths: 20mg and 80mg capsules
- Only available through Diplomat Specialty Pharmacy
  - Dispense Quantity = 112
  - Include ICD9 code/diagnosis

Drug Interactions
- Cabozantinib is a CYP3A4 substrate
- DDI with strong CYP3A4 inhibitors and inducers
- Food-drug interaction with grapefruit and grapefruit juice

Black Box Warnings
- Perforations and Fistulas
- Hemorrhage
Cabozantinib

- Most commonly reported ADE (≥25%)
  - Diarrhea
  - Stomatitis
  - Palmar-plantar erythrodysesthesia syndrome (PPES)
  - Decreased weight
  - Decreased appetite
  - Nausea
  - Fatigue
  - Oral pain
  - Hair color changes
  - Dysgeusia
  - Hypertension
  - Abdominal pain
  - Constipation

- Most common laboratory abnormalities (≥25%)
  - Increased AST, ALT, Alk Phos
  - Lymphopenia
  - Hypocalcemia
  - Neutropenia
  - Thrombocytopenia
  - Hypophosphatemia
  - Hyperbilirubinemia

- Serious ADEs
  - ONJ
  - RPLS
  - Pancreatitis
  - Nephrotic syndrome
  - Hemorrhage
  - Perforation/Fistula
Afatinib

- Targets: EGFR, HER2, HER4
- Use
  - 1st line NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations
- Dosing: 40 mg once daily on an empty stomach
- Drug Interactions: PgP

- Adverse effects (≥20%)
  - Diarrhea
  - Rash/dermatitis acneiform
  - Stomatitis
  - Paronychia
  - Dry skin
  - Decreased appetite
  - Pruritus
Afatinib

- Do not take a missed dose within 12 hours of next dose
- Women of reproductive potential should use highly-effective contraception during therapy and for at least 2 weeks after treatment has been discontinued
- Not yet available
2012 & 2013 Oncology Drug Approvals

Tara L. Chen, PharmD, BCOP
Helen M. Marshall, PharmD, BCPS, BCOP
PSONS Meeting
September 18, 2013
Axitinib

- Indication: Advanced renal cell carcinoma after failure of one prior systemic therapy
  - Multicenter Phase 3 study: Advanced RCC patients with progression on/after treatment with one prior therapy
    - Including sunitinib, bevacizumab, temsirolimus, or cytokine-containing regimens
  - Randomized to receive axitinib or sorafenib
  - Mean PFS 6.7 months in axitinib group vs. 4.7 months in sorafenib group
- Target: Kinase inhibitor; VEGFR 1, 2, and 3, PDGFR, cKIT
Axitinib

- **Dosing:** 5 mg PO Q12h, with or without food
  - May increase to 10 mg Q12h if no adverse effects > Grade 2 for two consecutive weeks
  - 50% dose reduction for Child Pugh Class B liver disease
  - Not studied in severe hepatic or renal dysfunction

- **Adverse effects as expected for VEGF, TKIs**
  - Impaired wound healing; proteinuria
  - Bleeding/hemorrhage; venous thromboembolism
  - Hypertension
  - Hand-food syndrome/rash
  - Thyroid dysfunction
  - Increased LFTs
  - Diarrhea, abdominal pain, GI perforation/fistula (rare)
Axitinib

- Drug & Food Interactions
  - Avoid grapefruit juice
  - Avoid CYP3A4 inducers (ex: phenytoin, carbamazepine)

- Available as 1 mg and 5 mg tabs

- Place in therapy
  - Patients who have failed at least one prior treatment
  - Firstline??
Bosutinib

• Indication: Chronic, accelerated, or blast phase Ph+ CML in patients with resistance or intolerance to prior therapy
  • Multicenter trial with patients in CP, AP, and BP previous treated with at least one TKI
    • Imatinib OR imatinib → dasatinib AND/OR nilotinib
  • Notable results:
    • 33.8% of patients in CP treated with one TKI achieved a major cytogenetic response (MCyR) at 24 weeks
    • In patients who had received > 1 TKI → 26.9% achieved MCyR
    • In AP CML patients treated with ≥ 1 TKI, 30.4% achieved complete hematologic response (CHR); 55.1% achieved overall hematologic response (OHR) by 48 weeks
    • In BP CML patients treated with ≥ 1 TKI, 15% achieved CHR; 28.3% achieved OHR by 48 weeks

CP = chronic phase; AP = accelerated phase; BP = blast phase; TKI = tyrosine kinase inhibitor
Bosutinib

- MOA: Inhibits BCR-ABL kinase. Also inhibits SRC family (including SRC, LYN, and HCK).
  - **Active in 16 of 18 imatinib-resistant BCR-ABL mutations**, with the exceptions of the T315I and V299L mutants

- Dosing: 500 mg PO daily with food
  - May increase to 600 mg/d

- Onset in responders
  - Median time to complete hematologic response (CHR) = 2 weeks
  - Median time to major cytogenetic response = 12.3 weeks
Bosutinib

- **Adverse Effects**
  - Fever
  - Fatigue
  - Rash
  - **Diarrhea (82%)**
  - N/V, Abdominal pain
  - Thrombocytopenia, anemia, neutropenia
    - HOLD bosutinib if platelets < 50k and/or ANC < 1000
  - Increased LFTs
  - Fluid retention (edema, pleural effusion, pericardial effusion)

- **Drug Interactions**
  - Avoid moderate/strong CYP3A4 inducers and inhibitors (ex: voriconazole, posaconazole, verapamil, grapefruit; phenytoin, carbamazepine)
  - Avoid PPIs (may use H2 blockers but separate by at least 2 hours)

- **Available as 500 mg and 100 mg tablets**
- **Dose reduce for hepatic dysfunction, diarrhea (≥ 7 stools/day), hematologic toxicity**
Ponatinib

- Accelerated approval

- Indication: Chronic phase, accelerated phase, or blast phase CML that is resistant/intolerant to prior TKI therapy; Ph+ ALL that is resistant or intolerant to prior TKI therapy
  - PACE trial – multicenter trial in patients resistant/intolerant to prior TKI therapy
    - CP CML: 54% patients achieved MCyR
    - AP CML: 52% patients achieved major hematologic response (MaHR)
    - BP CML: 31% patients achieved MAHR
Ponatinib

- MOA: Pan-BCR-ABL TKI with *in vitro* activity against cells expressing native or mutant BCR-ABL (including T315I); also inhibits VEGFR, FGFR, PDGFR, FGFR, EPH, and SRC kinases, as well as KIT, RET, TIE2, and FLT3

- Dosing: 45 mg PO daily, with or without food

- Available in 15 mg and 45 mg tablets
Ponatinib

- Black Box Warnings
  - Hepatotoxicity: Liver failure and death resulting from ponatinib-induced hepatotoxicity were observed; monitor liver function prior to and at least monthly (or as clinically indicated) during treatment
  - Thromboembolism: Cardiovascular, cerebrovascular, and peripheral vascular arterial thrombosis, including fatal myocardial infarction (MI) and stroke events, have occurred.

- Other serious ADEs: Myelosuppression, edema, GI perforation, heart failure/cardiac events, hemorrhage (cerebral and GI), hypertension, pancreatitis, TLS, impaired wound healing
Ponatinib

- **Adverse Effects (>25%)**
  - **Hypertension**
  - Fatigue, arthralgia
  - Headache
  - Fever
  - Rash
  - Dry skin
  - Abdominal pain
  - N/V/D, constipation
  - Mucositis

- **Drug Interactions**
  - Start at 30 mg daily for concomitant strong CYP3A4 inhibitors
  - Avoid CYP3A4 inducers
  - Avoid PPIs/H2 blockers/antacids

- **Lab Changes**
  - Increased glucose
  - Decreased phosphorus, sodium, calcium
  - Increased LFTs

- **Dose adjustments:**
  - Neutropenia/thrombocytopenia
  - LFT abnormalities
  - Pancreatitis, increased lipase
Omacetaxine mepesuccinate

- Accelerated approval

- Indication: Chronic or accelerated phase CML with resistance and/or intolerance to two or more TKIs
  - CP CML: 18.4% patients achieved MCyR
  - AP CML: 14.3% patients achieved MaHR

- MOA: Not fully known; inhibits protein synthesis. Acts independently of BCR-ABL1 kinase-binding activity. Has demonstrated activity against TKI-resistant BCR-ABL mutations

- Severe renal/hepatic dysfunction not yet studied
Omacetaxine mepesuccinate

- **Dosing**
  - *Induction*: 1.25 mg/m² SQ BID x14 days Q28 days; continue until hematologic response is achieved
  - *Maintenance*: 1.25 mg/m² SQ BID x7 days Q28 days; continue until no longer achieving clinical treatment benefit

- **Onset**
  - CP CML: Mean time to major cytogenetic response: 3.5 months
  - AP CML: Mean time to complete hematologic response: 2.3 months
Omacetaxine mepesuccinate

- **Adverse Effects (>25%)**
  - Fatigue
  - Fever
  - Nausea, diarrhea
  - Injection site reaction
  - Infection, including febrile neutropenia
  - **Hyperglycemia**
  - **Myelosuppression** (thrombocytopenia, neutropenia, anemia)
  - Hemorrhage (GI and cerebral) – rare

- Neutropenia grade 4 (ANC <500) or thrombocytopenia ≥ grade 3 (platelets <50,000) during a cycle
  - Delay the start of the next cycle until ANC ≥1000/mm³ and platelets ≥50,000/mm³ **AND**
  - Reduce the number of treatment days by 2 days

**NOTE:** No NSAIDs, aspirin, anticoagulants when Platelets < 50,000
Carfilzomib

- Accelerated approval

- Indication: Multiple myeloma patients who have received 2+ prior therapies, including bortezomib + immunomodulatory agent (IMiD), and have demonstrated disease progression on/within 60 days of completion of last therapy
  - Overall response rate = 22.9%
  - Median response duration = 7.8 months

- MOA: Proteasome inhibitor – potent, selective, and irreversible inhibitor of chymotrypsin-like activity of the 20S proteasome (intracellular protein homeostasis), leading to cell cycle arrest and apoptosis
Carfilzomib

- **Dosing (Max BSA of 2.2 m²):**
  - *Cycle 1:* 20 mg/m² IV on Days 1, 2, 8, 9, 15, & 16 Q28 days
  - *Cycle 2 and subsequent cycles (if cycle 1 is tolerated):* 27 mg/m² IV on Days 1, 2, 8, 9, 15, & 16 Q28 days
  - IV hydration strongly recommended, particularly for Cycle 1: 250-500 mL NS pre- and post-dose
  - Premedicate with dexamethasone 4 mg PO/IV prior to all doses in Cycle 1 and 2 (if dose increased), then PRN

- **Dose adjustments:**
  - Neutropenia/thrombocytopenia
  - Cardiac or pulmonary toxicity
  - Hepatotoxicity/LFT increased
  - Kidney dysfunction
Carfilzomib

- **Adverse Effects (>25%)**
  - Fatigue
  - Fever
  - Headache
  - Nausea
  - Anemia
  - Thrombocytopenia
  - **Dyspnea**
  - **URI/pneumonia**
  - Cough
  - 24% Peripheral edema and lymphopenia

- **Severe Adverse Effects**
  - Myelosuppression
  - Cardiovascular effects (MI, HF)
  - Hepatic failure
  - TLS
  - Infusion reactions
    - May occur up to 24 hours post infusion
  - Pulmonary arterial hypertension
Carfilzomib: Place in Therapy

- For patients who have failed bortezomib and an IMiD
- Other considerations & future directions
  - Firstline
    - Carfilzomib + Low-dose Dexamethasone + Lenalidomide
    - CLARION Study – Carfilzomib + Melphalan + Prednisone (CMP) vs. Bortezomib + Melphalan + Prednisone (VMP)
  - Prior to bortezomib as salvage?
    - ENDEAVOR Trial – Carfilzomib/Dexamethasone vs. Bortezomib/Dexamethasone
Pomalidomide

- **Indication:** Multiple myeloma patients who have received 2+ prior therapies (including lenalidomide and bortezomib), and have disease progression on or within 60 days of last therapy.
  - Multicenter study in relapsed/refractory MM, randomized to pomalidomide or pomalidomide + dexamethasone
  - Overall response rate = 7% (pom alone) vs. 29% (pom/dex)

- **MOA:** Immunomodulatory agent; inhibits proliferation and induces apoptosis of tumor cells, enhances T-cell and NK-cell-mediated immunity, possesses antiangiogenic activity

- **Dosing:** 4 mg PO daily, on empty stomach.
Pomalidomide

- **Adverse Effects**
  - **Black Box Warning:**
    - Embryo-fetal toxicity
    - Venous thromboembolism
  - **Myelosuppression**
    - Neutropenia Grade 3/4 = 43%
    - Febrile neutropenia 3%
    - Thrombocytopenia
    - Anemia
  - N/V/C/D
  - Fatigue
  - Rash, pruritus
  - Peripheral neuropathy
  - Dizziness, confusion

- **No clear dose adjustments for renal or hepatic dysfunction**

- **Cases of AML have been reported with pomalidomide use (outside of multiple myeloma indication)**

- **1mg, 2mg, 3mg & 4mg capsules**

- **Only available via Celgene’s REMS program due to teratogenic risk**
Pomalidomide: Place in Therapy

- Relapsed/refractory myeloma
  - Effective in lenalidomide-refractory patients
  - High remission rate in high-risk disease

- Maintenance agent?
# New Melanoma Agents

<table>
<thead>
<tr>
<th>Targets</th>
<th>Dabrafenib (Tafinlar)</th>
<th>Trametinib (Mekinist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF Mutation</td>
<td>V600E</td>
<td>V600E, V600K</td>
</tr>
<tr>
<td>Use</td>
<td>Metastatic or unresectable melanoma with V600E mutation</td>
<td>Metastatic or unresectable melanoma with V600E or K mutation; NOT for pts that received prior BRAF tx</td>
</tr>
</tbody>
</table>
| How Studied   | • Dabrafenib vs. Dacarbazine  
• Median PFS 5.1 months vs. 2.7 months, respectively | • Trametinib vs. chemotherapy  
(Dacarbazine or Paclitaxel)  
• Median PFS 4.8 months vs. 1.5 months, respectively |
| Administration| Oral, empty stomach | Oral, empty stomach |
| Dosing        | 150 mg PO Q12h        | 2 mg PO daily          |
| Common ADEs   | hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and **palmar-plantar erythrodysesthesis syndrome** | rash, diarrhea and lymphedema |
# New Melanoma Agents

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib (Tafinlar)</th>
<th>Trametinib (Mekinist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare/Serious ADEs</td>
<td>new primary skin cancers (cutaneous squamous cell carcinoma, new primary melanomas, and keratoacanthomas), febrile drug reactions requiring hospitalization, hyperglycemia, and uveitis/iritis</td>
<td>cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, interstitial lung disease and serious skin toxicity</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Avoid strong CYP3A4 inhibitors (ie, antiretrovirals) &amp; inducers</td>
<td></td>
</tr>
<tr>
<td>Febrile drug reaction</td>
<td>38.5-40°C → hold until temp normalizes, resume at same or reduced dose; &gt;40°C → hold until temp normalizes, resume at reduced dose or D/C</td>
<td></td>
</tr>
<tr>
<td>Dosage Forms</td>
<td>50 mg, 75 mg capsules</td>
<td>0.5 mg, 2 mg tablet</td>
</tr>
</tbody>
</table>
New Melanoma Agents

- Considerations
  - Broader molecular coverage with newer agents?
  - New mechanisms of resistance
  - Combining BRAF and MEK inhibition
  - Adverse events profile and patient selection
Questions?